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# Clonal spread of staphylococci among patients with peritonitis associated with continuous ambulatory peritoneal dialysis

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*Background.* Peritonitis is the most important complication of continuous ambulatory peritoneal dialysis (CAPD). Coagulase-negative staphylococci (CNS) are the most common causes of peritonitis, only limited information is available regarding the distribution and epidemiology of different CNS species associated with CAPD peritonitis.

*Methods.* CNS isolated from dialysis effluent from CAPD patients with peritonitis was identified by species and further analyzed with pulsed-field gel electrophoresis (PFGE).

*Results.* A total of 216 microorganisms (206 bacteria and 10 Candida species) were isolated from 196 consecutive culture-positive CAPD samples obtained from 75 patients. One hundred and twenty-one (56%) isolates represented staphylococci. The four most frequently isolated staphylococcal species were *Staphylococcus epidermidis* (70 isolates), *Staphylococcus aureus* (31 isolates), *Staphylococcus hemolyticus* (10 isolates), and *Staphylococcus hominis* (4 isolates). PFGE analysis revealed the clonal spread among patients of three different clones of *S. epidermidis* and one clone of *S. aureus* among the investigated patients. Indistinguishable isolates of either *S. epidermidis*, *S. hominis*, or *S. aureus* were also isolated in repeated samples from several patients.

*Conclusion.* PFGE is a useful method for the epidemiological evaluation of staphylococci-associated CAPD infections and should replace older and less accurate methods, such as antibiotic sensitivity patterns. We recommend that CNS isolates from patients with CAPD-associated peritonitis should be saved for future investigations and typing, which would aid in the management of this patient category.

Coagulase-negative staphylococci (CNS) are important pathogens in infectious peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD) [1, 2]. They are the most frequently isolated organisms in these infections, causing approximately half of the episodes of CAPD-associated peritonitis [1, 3, 4]. *Staphylococcus aureus*, on the other hand, is predominantly associated with tunnel and exit infections [3].

Despite the importance of different CNS species associated with clinical infections, limited information is available regarding their reservoirs, distribution, and mode of transmission among patients with CAPD [1, 2, 5]. Methods for molecular typing, such as pulsed-field gel electrophoresis (PFGE), have, however, been introduced during recent years, enabling epidemiological and pathogenic studies of CNS-associated peritonitis [2, 6, 7]. These new typing methods have proved to be more accurate than traditional methods, such as antibiotic sensitivity patterns [7]. The knowledge generated should be essential to improve methods of prevention, diagnosis, and therapy [2].

The aim of this study was to retrospectively evaluate the distribution of staphylococci species isolated from patients with CAPD peritonitis at our hospital during a 10-year period and to study the possible molecular relationship of these isolates within and among different patients with PFGE.

## METHODS

### Study design

Consecutive samples of peritoneal fluid were collected during a nine year period (1984 to 1993) from patients undergoing CAPD. An episode of peritonitis, symptomatic or asymptotic, was defined as the occurrence of turbid peritoneal fluid in combination with an increase in the leukocyte concentration in the peritoneal fluid. This was measured by either manual counting ($>100 \times 10^6$/L) or by dip-stick test score (score 2 or 3 by Ecur-test4; Boehringer Mannheim, Mannheim, Germany) in least two consecutive bags [8]. Samples were split in three parts: (*a*) 100 mL of the dialysate effluent was inoculated on blood agar plates incubated for 48 hours at 37°C in air and on modified Thayer-Martin agar containing Gc-medium Base, 36 g/L (Difco Laboratories, Detroit, MI, USA), hemoglobin 10 g/L, and IsoVitaleX 10 mL/L (BBL, Microbiology Systems, Cockeysville, MD, USA)

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and incubated for 48 hours at 37°C in 5% $CO_2$ in air; (*b*) 10 mL were centrifuged at 3175 × *g* for 10 minutes, and the sediment was inoculated on blood agar plates and modified Thayer-Martin agar as described previously in this article; (*c*) 5 mL were aseptically inoculated in biphasic culture bottles and incubated at 37°C in air for seven days with daily examination for growth.

### Species identification

Yeast and bacteria were identified by standard laboratory procedures [9]. Isolates of staphylococci were further identified to species level by a previously described typing system [5]. Staphylococcal isolates identified as species other than *S. epidermidis* were also tested with the simplified typing scheme described by Kloos and Schleifer [10] and the commercial ID 32 Staph typing system (BioMerieux sa, Lyon, France). When identical species were isolated from one sample occasion, only one isolate was included in the study. Isolates were stored at −70°C in 1 mL freezing buffer (saccarose 82 g/L, sodium glutamate 0.7 g/L, potassium dihydrogen phosphate 0.52 g/L, dipotassium hydrogenphosphate 1.25 g/L, and bovine albumin 25 g/L, pH 7.3)

### Antibiotic susceptibility testing

Antibiotic susceptibility was determined by an agar dilution method using multipoint inoculumn on PDM-ASM agar (Biodisc, Solna, Sweden). The agar plates contained different antimicrobial agents: penicillin G 0.2 mg/L (growth indicated β-lactamase production and correlated well to nitrocephine testing; data not shown), oxacillin 2 mg/L, clindamycin 2 mg/L, gentamicin 4 mg/L, cotrimoxazole 32 mg/L, and vancomycin 4 mg/L. The agar plates were inoculated and incubated at 37°C for 18 to 24 hours, except for oxacillin, which were incubated at 30°C.

To verify methicillin-resistant *S. aureus* (MRSA), 108 bacteria were inoculated on PDM-agar (Biodisc) containing 5% horse blood. An oxacillin disc (1 mg) was applied, and the plates were cultured at 30°C for 24 hours according to recommendations of the Swedish Reference Group for Antibiotics (http://www.ltkronoberg.se/ext/raf/raf.htm). Finally, the presence of the *mecA* gene was verified or excluded by amplification of the *mecA* and the *nuc* genes using the polymerase chain reaction (PCR) technique [11].

### Pulsed-field electrophoresis and gel electrophoresis

DNA was prepared from a 3 mL bacterial culture in Todd-Hewitt broth (Difco) and was incubated for 18 hours at 37°C. Of the overnight culture, 500 mL were centrifuged at 10,000 × *g* for one minute, and the pellet was washed in 500 mL of TN-buffer (10 mmol/L Tris-HCl, 1 mol/L NaCl, pH 7.6). The pellet was suspended in 100 mL TN buffer, and 100 mL 2% Low Melt Agarose (Bio-Rad Laboratories, Hercules, CA, USA) was added, mixed, and pipetted into plug molds (Bio-Rad), and allowed to solidify at 4°C for 15 minutes. The plugs were placed in 1 mL of lysis buffer (containing 10 mmol/L Tris-HCl, pH 7.6, 1 mol/L NaCl, 0.5% sarkosyl; BDH Laboratory Supplies, Poole, UK) and 1 mg lysozyme (Sigma Chemical Co., St. Louis, MO, USA), and 200 units of mutanolysin (Sigma) were added and incubated at 37°C for 210 minutes. The plugs were rinsed in 2 mL TE buffer [10 mmol/L Tris-HCl and 1 mmol/L ethylenediaminetetraacetic acid (EDTA) at pH 7.6]. To the rinsed plug, one mL of proteinase K buffer (containing 0.5 mol/L EDTA, pH 7.6, 0.5% sarkocyl) and 1 mg proteinase K (Boehringer) were added and it was incubated at 50°C for 18 hours. The plugs were then washed five times in 2 mL TE buffer for 60 minutes at room temperature and stored at 4°C.

The plugs were restricted with *SmaI* (MBI Fermentas, Villinius, Latvia). The restriction fragments of the digested DNA were separated by PFGE in a GenePath™ apparatus (Bio-Rad) using the program for *S. aureus* for 20 hours according to the manufacturer's instruction. Gels were stained in 0.5 mg/L ethidium bromide and were rinsed and photographed under ultraviolet illumination.

Bacterial isolates were defined as genetically "indistinguishable" if they showed an identical chromosomal DNA restriction pattern on PFGE and genetically "closely related" strains if their PFGE patterns differed by not more than three bands. Isolates differing by more than three restriction bands in PFGE were defined as "different" strains [6].

## RESULTS

A total of 196 samples from 75 patients was investigated. Repeated samples were obtained from 48 of the 75 patients (64.0%). The distribution of the 216 isolated microorganisms is shown in Table 1. Ten isolates were identified as yeast (4.6%), 148 as aerobic gram-positive bacteria (69.4%), 53 as aerobic gram-negative bacteria (24.5%), and 5 isolates as anaerobic bacteria (2.3%).

The frequency of antibiotic susceptibility among staphylococcal species is shown in Table 2. Oxacillin resistance was observed among 53 and 60% of isolates of *S. epidermidis* and *S. hemolyticus*, respectively. Resistance to antibiotics other than penicillin G was noted in only one isolate of *S. aureus.* No oxacillin-resistant *S. aureus* was found (Table 2). Eight staphylococcal isolates (5 *S. epidermidis*, 2 *S. hemolyticus*, and 1 unidentifiable CNS) were resistant to all antibiotics tested except for vancomycin.

Six isolates of *S. epidermidis* showing indistinguishable PFGE profiles were obtained from six different patients (Fig. 1). These patients were all treated at the same

**Table 1.** Distribution of 216 microorganisms isolated from 196 samples of peritoneal dialysis fluid effluent of 75 patients with continuous ambulatory peritoneal dialysis

| Yeast/bacteria | Aerobic/anaerobic bacteria | Gram strain | |
|---|---|---|---|
| | *N* | | Species |
| Yeast (10) | | | *Candida albicans* (8) |
| | | | *Candida glabrata* (1) |
| | | | *Candida guillermondi* (1) |
| Bacteria (206) | Anaerobic (5) | | *Bacteroides fragilis* (4) |
| | | | *Bacteroides* spp. (1) |
| | Aerobic (201) | Negative (53) | *Acinetobacter* spp. (2) |
| | | | *Citrobacter* spp. (3) |
| | | | *E. coli* (14) |
| | | | *Entetrobacter* spp. (13) |
| | | | *Klebesiella* spp. (10) |
| | | | *Proteus* spp. (2) |
| | | | *Pseudomonas aeruginosa* (4) |
| | | | *Psuedomonas maltophilia* (1) |
| | | | *Pseudomonas* spp. (1) |
| | | | *Serratia* spp. (3) |
| | | Positive (148) | *Bacillus* spp. (1) |
| | | | *Corynebacterium* spp. (3) |
| | | | Micrococci (1) |
| | | | Alpha-hemolytic-streptococci (4) |
| | | | Group B Streptococcus (1) |
| | | | Enterococci (17) |
| | | | *Staphylococcus aureus* (31) |
| | | | *Staphylococcus capitis* (1) |
| | | | *Staphylococcus epidermidis* (70) |
| | | | *Staphylocuccus haemoloyticus* (10) |
| | | | *Staphylococcus hominis* (4) |
| | | | *Staphylococcus saprophyticus* (1) |
| | | | CNS nonidentifiable (4) |

**Table 2.** Proportion of species and frequency of antibiotic resistance among 121 Staphylococci isolated from 54 patients with CAPD associated peritonitis

| | | | Number of antibody resistant (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Penicillin G | | Isoxazolyl penicillin | | Clindamycin | | Co-trimoxazole | | Gentamicin | |
| Bacterial species | *N* | Proportion % of all Staphylococci | *N* | (%) | *N* | (%) | *N* | (%) | *N* | (%) | *N* | (%) |
| *S. aureus* | 31 | 25.6 | 17 | (54.8) | 0 | (0.0) | 0 | (0.0) | 1 | (3.2) | 0 | (0.0) |
| *S. epidermidis* | 70 | 57.9 | 58 | (82.9) | 37 | (52.9) | 9 | (12.9) | 41 | (58.6) | 37 | (52.9) |
| *S. hemolyticus* | 10 | 8.3 | 8 | (80.0) | 6 | (60.0) | 2 | (20.0) | 5 | (50.0) | 5 | (0.0) |
| *S. hominis* | 4 | 3.3 | 1 | (25.0) | 0 | | 0 | | 1 | (25.0) | 0 | |
| *S. saprophyticus* | 1 | 0.8 | 0 | | 0 | | 0 | | 0 | | 0 | |
| *S. capitis* | 1 | 0.8 | 0 | | 0 | | 0 | | 0 | | 0 | |
| *CNS* nonidentifiable | 4 | 3.3 | 3 | (75.0) | 3 | (75.0) | 2 | (50.0) | 2 | (50.0) | 1 | (25.0) |
| *CNS total* | 90 | 100 | 70 | (77.8) | 46 | (51.1) | 13 | (14.4) | 49 | (54.4) | 43 | (47.8) |

dialysis unit and ward during a five-year period and in most cases also by the same team of physicians and staff. They were all hospitalized on several occasions and in some instances concurrently. The first three isolates were obtained within a three-month period, and the other three isolates three, four, and five years thereafter. Five different antibiotic profiles were found among these isolates. Two other "clones" of *S. epidermidis* showing indistinguishable PFGE profiles were also isolated from two and three different patients (within a 6-month period), respectively (Fig. 1). Moreover, two *S. aureus* isolates with indistinguishable PFGE profiles were found in samples obtained seven months apart from two different patients.

The 31 *S. aureus* isolates originated from 25 different patients. From four patients, more than one sample (range 2 to 4 samples) yielded growth of *S. aureus.* In one of these patients, a 70-year old woman, *S. aureus* was isolated from four consecutive episodes with clinical peritonitis during a 10-month period. The first, third (after 5 months), and fourth (after 10 months) of these isolates had indistinguishable PFGE profiles and antibi-

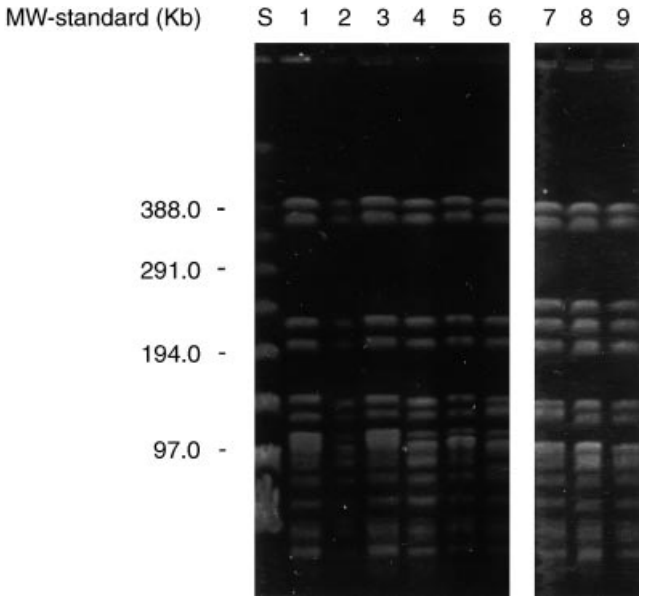


**Fig. 1. Pulsed field gel electrophoresis (PFGE) patterns of SmaI digested chromosomal DNA from 9 isolates representing two different clones of *S. epidermidis* isolated in the dialysis effluent obtained from 6 and 3 patients, respectively.** Lane S, molecular standard; lanes 1 to 6 represent isolates of *S. epidermidis* with indistinguishable chromosomal pattern obtained from 6 patients, lanes 7 to 9 are isolates of *S. epidermidis* with an indistinguishable chromosomal pattern obtained from 3 patients.

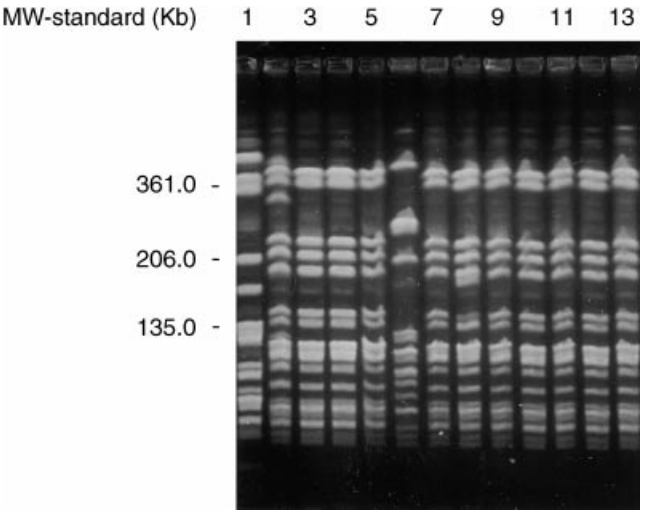


**Fig. 2. PFGE patterns of SmaI digested chromosomal DNA from isolates of 13 *S. epidermidis* found in 13 repeated samples of dialyze effluent from one patient.** Lanes 1 to 13 are chromosomal *S. epidermidis* DNA. Identical chromosomal DNA patterns are observed in lanes 3 to 5 and 7 to 13. A closely related chromosomal pattern is in lane 2, and non-identical chromosomal patterns are in lanes 1 and 6.

otic-resistance patterns, whereas the second isolate (after 2 months) differed in both PFGE profile and antibiotic susceptibility. Treatment with intraperitoneal cefuroxime was instituted on each occasion with the initial clinical response. Removal of the dialyze catheter was planned during the last episode of peritonitis, but the patient succumbed because of stroke. In another patient, *S. aureus* with indistinguishable PFGE profiles was found in two consecutive samples (only 4 days apart), whereas the other two patients were infected on separate occasions with isolates exhibiting different PFGE profiles.

The 70 *S. epidermidis* isolates originated from 37 different patients. From 12 patients, more than one sample (range 2 to 13 samples) yielded growth of *S. epidermidis.* In seven of these patients, *S. epidermidis* isolates with indistinguishable PFGE profiles were found in repeated samples (range 2 to 10 samples). In one patient, *S. epidermidis* was repeatedly isolated from 13 samples during a three-month period. Of these 13 isolates, 10 showed indistinguishable, 1 a closely related, and 2 different PFGE profiles (Fig. 2). The 10 isolates with indistinguishable PFGE pattern exhibited three different antibiotic-resistance patterns. This patient, a 25-year-old diabetic, had four episodes of clinical peritonitis with positive cultures of *S. epidermidis* during a four-month period. He was hospitalized on each occasion and treated with various antibiotics on the three first occasions according to results of the antibiotic sensitivity testing. The dialyses catheter was replaced during the first episode of peritonitis. He was on each of the three first episodes treated until clinical signs of infection had resolved and negative cultures had been obtained yet symptoms relapsed. The infection eventually resolved after intraperitoneal treatment with vancomycin for 10 days and a two-month follow-up with oral clindamycin.

The 10 *S. hemolyticus* isolates originated from nine different patients. All isolates had different PFGE profiles, and eight different antibiotic resistance patterns were found among these isolates. In one patient, *S. hemolyticus* with nonidentical PFGE profiles was isolated twice during a period of four years. *S. hominis* was isolated from three patients. Isolates with indistinguishable PFGE profiles were obtained from one patient on two separate occasions.

## DISCUSSION

Our study showed that species identification combined with PFGE is a useful method for epidemiological evaluation of staphylococci-associated CAPD infections. According to PFGE analysis, clonal spread of staphylococci occurred among patients undergoing CAPD at our hospital. The clonal spread of CNS among patients with CAPD peritonitis has, to our knowledge, not previously been described. Interpatient transmission of CNS isolated from CAPD patients with peritonitis was not detected in another study evaluating 41 biochemical identical isolates of CNS with a DNA fingerprinting method [12]. The results imply that clones of CNS may reside in

the environment and/or among staff for long periods of time. Further prospective studies, including cultures from the environment and staff, are required to answer questions regarding the possibility of nosocomial spread of staphylococci in dialysis wards. Other studies have demonstrated the clonal spread of CNS among patients and staff in other types of ward units [13, 14]. The spread of staphylococci in ward units may be related to staff—patient transmission, environmental contamination, or (more unlikely) patient—patient transmission.

It is apparent from our results that CAPD-associated infections with a specific clone of CNS may persist over long periods of time, whereas other patients are infected with genetic variants of the same phenotypic CNS species, as well as different CNS species. The results strongly indicate that phenotypic identification and antibiotic sensitivity analyses are of limited value for epidemiological evaluation of CNS. Without PFGE, it would have been impossible to state whether patients had persistence/relapse or a reinfection with new strains. Older methods should be replaced by more sensitive molecular typing methods, such as PFGE, because they can detect persistent clonal infections in a given location.

Our findings support previous proposals that bacteria isolated from patients with CAPD-associated peritonitis should be stored for future investigations and typing, which most certainly would aid in the management of this patient category [15, 16]. The information generated should be of value for choice of antibiotic treatment, as well as in the decision of catheter removal or replacement. The usefulness of PFGE in epidemiological studies of staphylococci-causing CAPD infections was recently illustrated in publication investigating *S. aureus* isolates with decreased sensitivity for vancomycin [16].

It should be remarked that PFGE requires specialized equipment and personnel, which may limit its use routine practice. Nevertheless, PFGE is nowadays an established method for molecular typing of many bacteria, including staphylococci [6, 7, 16]. Until the practical application of PFGE has been further elucidated in prospective studies, we suggest typing of strains isolated from patients with persistent or recurrent infections. This requires the use of adequate culture technique [17] and methods for storage of bacteria (detailed in the **Methods** section). We also believe that that periodic surveillance of patients and staff on specific wards could be useful in order to avoid the spread of multiresistant bacteria within the hospital environment [16]. The cost for analyses of one isolate at our laboratory is approximately $40 (U.S. dollars).

Antibiotic susceptibility among the staphylococcal isolates in this study was similar to that observed among bloodstream isolates of staphylococci at our hospital and other parts of Scandinavia [18]. Sweden has a low prevalence of MRSA (<1% of clinical isolates) compared with many other Western countries. Oxacillin resistance among clinical isolates of CNS is, however, a common finding also in Sweden, and the frequency observed here (53%) was similar to that reported in number of studies from Europe and the United States [18, 19].

We conclude that monitoring of CNS-associated CAPD infections with species identification and PFGE analyses could provide important information regarding the nosocomial epidemiology of these bacteria. With the aid of these methods, we could demonstrate persistent infections and clonal spread of *S. aureus* and CNS among patients. The introduction of this method in the routine laboratory analysis of selected patients could substantially aid in the monitoring and management of individual patients with CAPD-associated infections.

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